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SPECIAL ARTICLE

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Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care

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Abstract Our objective in this study was to summarize the relevant knowledge on depression in palliative care and to provide a framework for clinical, scientific and educational efforts at improving its management. The Research Steering Committee (RSC) of the European Association of Palliative Care (EAPC) established an Expert Working Group (EWG) to address the issue of depression in palliative care. Each invited expert was allocated a specific topic and was asked to review the literature. These reviews were presented during the Sixth Congress of the EAPC in 1999 and then discussed in a closed meeting with members of the RSC. Based on these reviews, and the discussions that followed their presentation, a first draft of the paper was produced and circulated among the invited experts and members of the RSC who had been present at the meetings. After some debate the manuscript was revised, and a second draft was circulated, this time also to RSC members who had not attended the meetings. All persons consulted have agreed on this final version of the report. The EWG concluded that the current level of evidence did not lend itself to the development of clinical guidelines and decided to publish the results of their work as a pragmatic report. The report is divided into four sections, focusing on detection, training and nonpharmacological and pharmacological treatment of depression in palliative care. For each of these sections, general considerations are addressed on the basis of the literature review and of clinical experience and a short description of unresolved issues and recommendations is provided. Underdetection and undertreatment of depression is a serious problem in palliative care. Training of the nonpsychiatric staff should therefore have the highest priority. A proactive, flexible and comprehensive strategy embracing clinical, scientific, and educational aspects is advocated.

Keywords Depression · Palliative care · Detection · Treatment · Staff training

Introduction

The European Association for Palliative Care (EAPC) is a multiprofessional association for persons involved in palliative care. The EAPC has specific networks for issues related to education, ethics, policy questions and research. The Research Steering Committee (RSC) of the research network of the EAPC initiates Expert Working Groups (EWG) to address specific topics, to summarize relevant knowledge, to develop recommendations, and to identify priorities for future research. So far, the topics covered by EWGs have been concerned with morphine administration [38], pain assessment tools [13], breakthrough cancer pain [65], management of bowel obstruction [83], the use of corticosteroids in palliative care [28], and strategies to manage adverse effects of oral morphine [15].

The meetings of the EWG on Depression in Palliative Care were held during the Sixth Congress of the EAPC in Geneva (22–24 September 1999). In four open workshops[1] the invited experts reviewed relevant aspects of depression in palliative care, with particular reference to detection, training, and nonpharmacological and pharmacological treatment. A closed meeting with the experts and members of the RSC was organized a day after the congress to discuss these topics in detail. A first version of this paper summarizing the presentations and the subsequent discussions was drafted by the Chair and circulated to the Co-Chair, the invited experts and the members of the RSC who attended the closed meeting. After revision, a second version circulated, this time also to members of the RSC who had not been able to attend the closed meeting. Only unanimous conclusions have been included in this final version, which is based as far as possible on scientific evidence. Since a large part of the knowledge on this topic is not yet supported by scientific evidence, the EWG concluded that the current level of evidence did not lend itself to the development of clinical guidelines [110]. The results of the work are therefore presented as a pragmatic report based on a literature review by the invited experts, their clinical experience, and the expertise of the members of the RSC. The literature review was provided by the experts and completed by the Chair with the aid of such conventional sources as Medline. The review cannot therefore be regarded as exhaustive. For each of the aspects specified above a summary of relevant knowledge will be presented, followed by an account of the unresolved issues and the recommendations for clinical practice and future research. The aim of the paper is to provide a framework for clinical, scientific and educational efforts to improve the management of depression in palliative care.

[1] The workshops were chaired by F. Stiefel and co-chaired by J.M. Nunez Olarte. "Detection of depression in palliative care" was presented by D. Razavi, "Psychotherapeutic treatments" by M. Die Trill, and "Pharmacological treatments" by A. Berney. "Educational aspects" was presented by D. Vuille (replacement) and then discussed by F. Stiefel

Background

The topic "depression in palliative care" was chosen by the RSC because psychiatric disorders are frequent in palliative care, often remain undetected and untreated, and add considerably to the burden of suffering on patients who are already facing severe physical and psychosocial problems [77, 94]. The RSC considered the topic "psychiatric disorders in palliative care" was too broad to be treated by an EWG and decided first to address a specific disorder and then utilize a similar approach for other psychiatric disorders frequently observed in palliative care. Since most of the literature on depression in palliative care is related to adult cancer patients and most of the patients in palliative care suffer from malignant diseases (WHO [112]), this paper draws largely on experience with adult cancer patients. However, there are many other diseases, such as cardiovascular, neurological, metabolic and rheumatological diseases, in which depression is also a relevant topic. The recommendations – with modifications where necessary – should therefore also be useful for patients with nonmalignant diseases. In addition, this first EWG on a specific psychiatric disorder in palliative care could serve as a model for other EWGs addressing psychiatric disorders of pediatric and geriatric patients.

General aspects of depression in palliative care

Two major paradigms exist in current clinical practice for defining depression: (1) the general phenomenon of depressive symptoms and (2) specific depressive disorders defined by diagnostic criteria [104]. While the general medical sector tends to conceptualize depression according to the former definition, a large proportion of mental health specialists conceptualize depression according to the second one [82]. These two paradigms have different implications for clinical care and treatment response. For example, antidepressant treatment has proved to be beneficial for patients with depression, but not for those with a depressive symptomatology attributable to an adjustment disorder [5]. The EWG was given a mandate to focus on major depression in palliative care and has therefore based its work on the established diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association [1], the most widely used diagnostic system (Table 1).

The prevalence of depression in palliative care varies, depending on type and stage of disease, setting and population characteristics [62], and has been reported as 3.7–58% [11, 21, 99]. Among hospitalized cancer pa-

Table 1 DSM-IV criteria of major depressive episode.[a] Five (or more) of the following symptoms[b] have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

– Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g., appears tearful)
– Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observations made by others)
– Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
– Insomnia or hypersomnia nearly every day
– Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
– Fatigue or loss of energy nearly every day
– Feelings of worthlessness or excessive and inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
– Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
– Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

[a] Adapted from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA)
[b] The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms are not due to direct physiological effects of a substance or a medical condition, and are not better accounted for by bereavement

tients with significant levels of physical impairment, at least one quarter of patients with advanced disease suffer from a clinically relevant and treatable depressive illness [7, 53, 54, 75, 102]. Unfortunately, only a minority of these patients receive the necessary pharmacological treatment [53, 59, 95]. The undertreatment of depression has different reasons [5, 6]. Among them are the difficulties of physicians to talk with patients about their emotions [61], or the belief – even among mental health professionals – that depression is somehow inevitable in the terminally ill [25]. It is unfortunate that health care professionals and the public agree that depressive illness should be treated in the physically healthy but remain skeptical about the treatment of depression in patients with severe somatic diseases.

In the palliative care setting depression and pain often coexist and influence each other. A close correlation between long periods of pain and depressive feelings has been demonstrated, a correlation that may be due to neurotransmitter changes, but also to psychological exhaustion [93]. On the other hand, pain-free periods are known to give patients new strength and to lower the incidence of mood disturbances and suicidal ideation [85]. It is very difficult to establish a diagnosis of depression in an individual suffering from unrelieved pain, and pain perception on the other hand may be influenced by depressed mood. Many of the symptoms of depression, such as sleep and appetite disturbances or loss of energy and fatigue, are also associated with unrelieved pain and disappear when analgesia is achieved [9]. Adequate treatment of pain is therefore most important in the management of depression in palliative care.

Detection of depression in palliative care

The undertreatment of depression in palliative care is closely related to the fact that depression remains undetected in a substantial number of patients [72, 99]. Some studies have found that depression remains unrecognized in more than 50% of depressed medically ill patients [56, 69]. The difficulty lies in differentiating depression from other psychiatric disorders, such as acute stress reactions or adjustment disorders and from normal reactions such as grief, or from somatic states that may mimic depression [16]. The psychiatric interview, conducted by an experienced consultation-liaison mental health professional who is familiar with patients with advanced disease, would certainly be the gold standard for detection of depression in this patient population [29, 75]. However, in most settings mental health specialists are not part of the palliative care team or their number is very limited. Detection of depression in palliative care by the treating physicians and nurses is therefore crucial.

The medical staff need specific knowledge, skills and instruments to detect depression in palliative care. Training in psychiatric issues is complex, however, and various factors hamper effective educational efforts (see section on Training, below). Most scientific approaches to the problem have concentrated on the use of screening instruments to detect depression. Screening is designed to detect a given disturbance early; it picks up false-positive and false-negative cases and is not diagnostic in confirming caseness. The instrument that has been most widely utilized and evaluated in the palliative care setting is the Hospital Anxiety and Depression Scale

(HADS) [113]. This self-report scale is especially suitable for the medically ill, since it does not include the somatic symptoms of depression, such as fatigue, pain or insomnia, which may also be caused by the illness or its treatment [60]. Several studies have concluded that the HADS is a simple, sensitive and specific tool that can be used to screen for adjustment, depressive, and anxiety disorders [37, 51, 52, 79]. However, there are several problems associated with the use of the HADS in daily clinical practice. First, the sensitivity and specificity of the instrument depends on cut-off points, which may change in different patient populations (e.g. inpatients, outpatients, young and elderly patients, patients differing in stage and type of disease) [45, 76]. Second, as with any other instrument, higher sensitivity is associated with lower specificity and higher specificity with lower sensitivity. Third, the HADS is a screening instrument for adjustment disorders with anxious and depressed mood, as well as for major depression or dysthymic and anxiety disorders. Since the types of intervention needed to treat these disorders differ, the HADS lacks a diagnostic component that would allow the diagnosis of major depression. Fourth, the HADS is an instrument based on self-report: acute stress reactions contribute to relatively high rates of false-positive results and social desirability, to false-negative results [96]. Its suitability for use as a screening instrument for depression in palliative care has therefore been called in question [35].

There are studies comparing different screening instruments [43, 45, 52], such as the HADS [113], the Zung Self-Rating Depression Scale [24], the General Health Questionnaire (GHQ) [30], and the Rotterdam Symptom Checklist (RSC) [20]. However, the aforementioned problems associated with screening remain the same. Diagnostic instruments for the detection of psychiatric disorders, including depression, also exist. The Prime MD – to mention one widely used and validated instrument – has been designed to diagnose six major psychiatric disorders (including depression) prevalent in primary care and consists of a one-page patient questionnaire and a structured diagnostic interview conducted by the physician [91]. This instrument has not been adapted and validated for palliative care. A two-step screening and diagnostic procedure for depression in palliative care has not yet been developed.

Unresolved issues

When all these difficulties associated with screening are taken into account, it becomes clear that no suitable instrument is available for the detection of depression in palliative care. Several issues therefore remain unresolved (Table 2). It remains unknown whether training in how to diagnose depression may be an alternative to the use of screening instruments or whether screening should be implemented as an isolated act. It also remains unclear whether screening should focus on specific disorders, how often it should be repeated over time, and how the somatic symptoms of depression should be taken into account. In addition, the screening of patients who are unable to communicate because of language barriers, personality traits or severe depressive states also remains an unresolved problem. The inter- and intraindividual variations in the threshold of psychological suffering and adaptation make it impossible to conceive of screening as a one-point procedure [78, 79]. Finally, the roles of the specialist nurse clinician [102] and of the consultation-liaison mental health professional have to be defined. In one study only 3 out of 106 patients receiving antidepressants were referred to mental health specialists [53].

Table 2 Detection of depression in palliative care: unresolved issues

Should efforts concentrate on screening instruments or on comprehensive, educational strategies?
Are specific mental disorders or “psychological distress” the focus of detection?
Since detection is not a one-point procedure, how should it be conceptualized longitudinally?
How can somatic symptoms of depression be taken into account in a medically ill patient population?
Intra- and interindividual variations in symptom thresholds, language barriers and personality traits hamper uniform detection procedures
The roles of the specialized mental health professionals remain undefined

Several other factors affect the diagnosis of depression. Among them are the diagnostic criteria: if diagnostic criteria differ, prevalence rates will of necessity also differ [47]. The same holds true for symptom severity thresholds, which may differ depending on instruments and clinical judgments [107]. In addition, inclusion and exclusion of somatic symptoms of depression or their substitution with psychological symptoms affect diagnosis prevalence rates. A flexible approach could be to exclude physical symptoms in the diagnosis of depression if they are probably due to physical disease or its treatment and to include them if they are more likely to be part of the depressive symptomatology [8].

Recommendations

As mentioned above, empirical studies addressing these questions are lacking; the following recommendations are therefore based on the clinical experience of the EWG and the literature (Table 3). Since palliative care settings vary widely with regard to patients and health care delivery characteristics, recommendations for the detection of depression also vary. For example, ambula-

Table 3 Detection of depression in palliative care: recommendations

The setting (patient and care delivery characteristics) should influence detection strategies; flexibility is most important
The "wait-and-see" policy should be replaced by a proactive strategy characterized by "trial and error"
Implementation of screening should be complemented by training and a comprehensive management strategy
Close collaboration with specialized mental health professionals from consultation-liaison psychiatry is mandatory
Comparison of different strategies should be the focus of future research
Referral policy to mental health professionals should be defined depending on the local circumstances

tory patients would have to be screened with different threshold levels than would inpatients, and any referral policy will depend on existing resources in terms of mental health specialists. Nevertheless, the current policy of "wait and see" should be replaced by a proactive clinical, scientific and educational strategy characterized rather by "trial and error." All screening procedures should be complemented by staff training and by close cooperation with consultation-liaison psychiatry. Consultation-liaison psychiatry services are usually staffed by mental health specialists from different professional backgrounds, such as psychiatry, psychology, nursing and social work. With regard to future research, comparison of different strategies should be favored, for example, implementation of screening or diagnostic instruments versus training in clinical judgement. Definition of local referral policies is also recommended.

Staff training

The assessment and treatment of psychiatric disorders depend on the ability to address sensitive issues, such as emotional states, illness representations, and relationships, which it may be difficult to ask about in patients with advanced disease. The highest levels of agreement between patients' self-reported depressive symptoms and staff members' perceptions are found when patients report few or no depressive symptoms, with only 14% concordance in the severe ranges of depression [64]. These results are similar to those of studies on the correlations between patients and health care professionals in their perception of pain [93], illustrating that adequate assessment is based on communication and not on intuition alone. Communication, on the other hand, is not just a natural gift, but can be influenced and improved by training [26, 58, 80]. Other important aspects of training are related to staff members' knowledge about how to diagnose depression, how to identify underlying etiologies, including organic factors, and how to differentiate depression from normal and other pathologic states. While the link between diagnosis and treatment of depression may seem obvious, clinical experience and scientific evidence from noncancer populations indicate that less than a quarter of diagnosed depressed patients receive effective treatment [3, 67]. In advanced disease this percentage is probably even lower, since the reluctance to prescribe antidepressants seems to be even greater in such patients [53]. Finally, monitoring of treatment and its adverse effects is often neglected and delays the reaction (changes of treatment modalities) to nonresponsiveness. In summary, many different factors hamper effective management of depression in palliative care and make training of the staff necessary. They can be identified as recognition barriers, diagnostic barriers, and treatment barriers related to patients, physicians, or health care system characteristics [31].

Up to now, only a few projects and studies have addressed the issue of training in the management of depression for nonpsychiatric health professionals [72]. While physicians seem to be aware of their need for improvement in diagnosing depression, effective strategies are difficult to design and to evaluate [36]. In a randomized study, a brief educational intervention did not significantly improve residents' ability to detect depressed patients; nevertheless it had changed the residents' attitudes and knowledge relevant to the care of depressed patients by the time they were followed up 6 months later [50]. In another randomized controlled trial, the training of specialist nurses led to a six-fold improvement in their ability to recognize patients with depression compared with nurses who had not had the training; the psychiatric referral rate increased five times, with a three- to four-fold reduction in the incidence of depression in the intervention group [58]. However, the accumulating load on specialist nurses and the tendency to delegate psychological care are major disadvantages of such models. It has also been demonstrated that specific interviewing behaviors, such as posing open-ended questions, periodically summarizing the information supplied by the patient, and responding to nonverbal and emotional cues, led to greater recognition of depression [2, 84]. These findings support the view that training in communication skills promoting such an interview behavior is important. In the Groningen Primary Care Study recognition of psychological disorders was not associated with better patient outcome; the authors concluded that recognition was necessary, but not sufficient, unless primary care physicians had the skills to provide appropriate treatment [100]. This view has been supported by other studies [31, 48]. Comprehensive strategies are therefore needed, and the provision of an antidepressant algorithm [18] or of diagnostic criteria alone seems not to be sufficient. First studies investigating comprehensive educational strategies designed to improve detection and treatment of depression in the physi-

cally ill are currently under way [72, 73]. Such comprehensive strategies should also define referral policies for mental health staff by outlining the limits of nonpsychiatric competence. If staff members encounter difficult cases, for example if there is diagnostic uncertainty, suicidality, an important psychiatric comorbidity or unresponsiveness to treatment, referral to specialized mental health professionals should be the rule [6].

Unresolved issues

Unresolved issues in staff training are listed in Table 4 and include the following. First, the lack of trained mental health specialists who are interested in palliative care remains a serious problem, especially with regard to training. Historically, psychiatry and somatic medicine have developed separately, and the emergence of psychiatric liaison services in general hospitals is relatively recent. Such services exist mainly in large hospitals and those affiliated to universities [109]. This lack of mental health specialists hampers educational efforts despite the strong support for interdisciplinarity within the palliative care movement. Second, even in settings where mental health specialists are part of the palliative care team, the choice of training strategies for the detection and management of depression are based on personal preferences and skills. Working with personal preferences may involve such advantages as increased motivation of the trainer, but they may not meet the needs of the staff, in which case they will be ineffective. Finally, the question remains whether patients, family members, nurses, physicians or other team members should be the target of training interventions. It also has to be determined whether communication skills, diagnostic skills or prescription behavior should be their main focus of these interventions. Such studies are difficult to conduct, since they involve both health care professionals and patients and outcomes are influenced by a variety of confounding variables.

Recommendations

Based on the studies reviewed and on clinical experience, the transfer of knowledge (e.g. of diagnostic criteria) alone may be a necessary but not a sufficient condition of improvement in the management of depression in palliative care. Other important training aspects concern the staff's ability to develop appropriate communication skills. The EWG therefore recommends complementing the transfer of knowledge with training in communication skills. Such training courses have proved to be effective if their duration and content are adapted to the type of work performed and if they are consolidated over time [80]. Finally, the EWG recommends that future research should focus on the evaluation and comparison of different, comprehensive training interventions. Again, close collaboration with specialized mental health professionals from consultation-liaison psychiatry (CL-Psychiatry) is especially crucial (Table 5).

Table 4 Staff training in the management of depression in palliative care: unresolved issues

How should the "transfer of knowledge" be organized given the lack of mental health professionals working in palliative care?
What are the most effective strategies for the training of nonpsychiatric staff?
Who should be the main target of training interventions and what should be their main focus?

Table 5 Staff training in the management of depression in palliative care: recommendations

Transfer of knowledge is a necessary, but not sufficient, element
Education should also include training in communication skills
Future research should compare different educational interventions

Nonpharmacological treatments

Prior to the discussion of treatment, the issue of prevention will be addressed. Since depression is associated with different factors, such as psychological and physical symptom distress, ineffective coping styles, and poor social support [17, 24, 37, 46, 70], preventive interventions could possibly have an impact. Up to now such attempts have not been very successful. In nontargeted interventions, a reduction in depression scores for patients in psychoeducational groups was achieved; the reduction did not seem to be clinically significant [27]. The same holds true for other interventions, which failed to reduce the incidence of depression [12, 32, 105, 111]. In order to have an impact, preventive interventions will most probably have to be targeted at patients at risk.

Treatment of depression should not be restricted to the prescription of a psychotropic medication. The empathy and support of significant others and of the medical team are as important as the psychopharmacological treatment [33, 77]. In addition to basic but very important nonspecific therapeutic interventions, such as support and information, specific psychotherapeutic interventions have been proposed for the treatment of depression in patients with severe and life-threatening diseases [19, 27, 89, 90]. However, only in a few studies on psychotherapy in the medically ill has the methodology been comprehensively described. Information on such important aspects as how randomization was achieved or how sample size, power and confidence intervals were calculated is most often lacking [23]. It is difficult to compare these studies, since timing and duration of interventions

vary, description of the practitioners providing the interventions is lacking, and study samples and outcome measures differ. Despite these difficulties, a recent meta-analysis of 30 trials of psychological interventions in depressed patients with cancer (10 trials were excluded because of missing data) demonstrated that interventions targeted at patients at risk or with significant psychological distress were associated with clinically powerful effects; group therapy was found to be more effective than individual therapy [87].

Most of the studies demonstrating the efficacy of psychotherapeutic techniques in depressed patients with cancer are based on group formats and cognitive-behavioral, time-limited models that have emphasized coping strategies, psychological strengths, personal control, relaxation training and cognitive restructuring [19, 27, 89, 90]. Some psychotherapeutic models have combined structured cognitive behavioral techniques with an existential approach [89], while others have reported the efficacy of a treatment package combining behavioral and pharmacological therapies [40]. Even though structured treatments have proved to be more effective in the reduction of depression than nonstructured treatments [68], clinical experience suggests that more psychodynamically oriented treatments may also be beneficial in the palliative care setting [33].

Table 6 Nonpharmacological treatment of depression in palliative care: unresolved issues

Preventive interventions will have to be targeted, but the profile of patients at risk for depression remains unknown
Many methodological aspects (e.g., concerning outcome) of psychotherapeutic intervention studies, are still controversial, and many of the studies in the palliative care setting have methodological flaws
Efficacy of psychotherapeutic interventions has been demonstrated, but effectiveness studies are still lacking
Nonspecific elements of psychotherapeutic interventions, such as empathy, favoring emotional expression and information are known to be beneficial, yet remain to be evaluated

Table 7 Nonpharmacological treatment of depression in palliative care: recommendations

Implementation of psychological treatments should be based on clinical and scientific evidence at this point in time
Training of nonpsychiatric staff (see recommendations for training) is currently the most effective strategy to improve the situation of the depressed patient in palliative care
Future research should focus on effectiveness studies and the unspecific therapeutic elements that can be offered by nonpsychiatric staff
Psychotherapeutic efforts should also include the patients' significant others

Unresolved issues

Before we can rely exclusively on scientific evidence when implementing psychotherapeutic programs in palliative care, the following issues need to be considered (Table 6). First, preventive interventions cannot yet be conceptualized. Second, it is necessary to ask whether the quantitative approaches used for the scientific evaluation of psychotherapeutic interventions are optimal for studying the complex topic of psychotherapy with patients who are facing the highly individual and existential issues of life and death. Outcome measures of depression that define the "success" of a given intervention in palliative care have yet to be defined. Third, it remains unknown whether psychotherapeutic interventions, such as group therapies and structured treatments implemented by trained counsellors that have been empirically tested, are beneficial for the majority of patients or whether they should be used in selected populations in specific clinical and cultural embeddings [19]. Fourth, a final interesting question concerns the key elements of psychotherapeutic interventions. It is well known from psychotherapeutic research that many nonspecific factors common to different interventions, such as empathy, providing information and support, and mutual emotional involvement, are key elements of psychotherapeutic progress [44, 86, 92]. Given all the reasons described above and the complexity of the palliative care patients, highly structured treatment modalities have to be regarded with caution despite the empirical evidence of their usefulness [97].

Recommendations

It is suggested that at this point in time, the implementation of psychological treatment should not be based on scientific evidence alone, and both highly structured psychotherapeutic treatments and other treatment modalities for which there is clinical although not yet empirical evidence of effectiveness can be recommended. In view of the persisting lack of mental health professionals working in palliative care, training of the nonpsychiatric staff is currently the most effective strategy to improve nonpharmacological treatment of the depressed patient with advanced disease. The above-mentioned training in communication skills is a basic requirement in reaching this goal; however, it is only one element in improving the psychological care of the depressed patient in palliative care. Future research should focus on the effectiveness and role of nonspecific elements of the psychotherapeutic process. Owing to the high levels of depression in significant others of patients in palliative care [39], they too, should benefit from these efforts (Table 7).

Psychopharmacological treatment

In most cases, management of major depression also involves pharmacological treatment. There has been considerable progress in the development of new antidepressants with a more favorable side effect profile facilitating their use in the medically ill and the elderly [5, 66]. Despite these developments, clinical utilization of these substances remains stable over time and is restricted to a small minority of patients with advanced disease [95]. A recent study on the prescription of antidepressant medication in palliative care found that only 10% of the patients admitted to a palliative care inpatient unit were treated with an antidepressant. In the majority of cases, the medication was initiated during the final 2 weeks of life, consequently leaving insufficient time for the medication to have any therapeutic effect [53]. Barriers to the use of antidepressants derive from the patient (e.g., lack of compliance, fear of side effects) or from the physician (e.g., lack of training, unfamiliarity with these substances) [49].

Thus, there is a considerable gap between the progress in the development of newer antidepressants and their utilization. Even when the diagnosis of depression has been established and initiation of psychopharmacological treatment seems obvious, less than a quarter of depressed psychiatric patients receive effective treatment [31, 67]. It is difficult to imagine that the situation in the palliative care setting is any better. Although there are many reports on the efficacy of antidepressants in depressed patients with advanced somatic disease, only a few controlled studies have been conducted [5]. These placebo-controlled double-blind studies support the clinical experience indicating that these substances improve depressive symptoms and quality of life [41, 81, 103]. If such treatment is indicated, these medications should be prescribed in a dose that guarantees therapeutic efficacy (therapeutic range). Medications should be changed if there is no appropriate response after a 2- to 3-week treatment period with a therapeutic dosage [5]. After resolution of the depressive state, they should be continued for at least 4–6 months and slowly tapered [88].

The era of antidepressants started with agents with effects on multiple receptor systems, then progressed to selective agents with single pharmacological mechanisms, and we now have drugs that again offer multiple receptor actions but also selective mechanisms, reducing side effects while maintaining clinical efficacy [5]. Because older and newer antidepressants are equally efficacious [88, 106], both adverse effect profiles and pharmacological properties (half-life, interactions, accumulation in hepatic and renal impairment) should determine the one selected. The newer (serotoninergic) agents have fewer side effects; some of them are available in liquid forms for patients with difficulties in swallowing and can be considered as first-line treatment in the presence of medical illness [4]. Tricyclics or tetracyclics (mianserin) may still be useful, for example in patients with concomitant insomnia and neuropathic pain [57]. The reader is reminded that tricyclic agents have anticholinergic and antihistaminic properties and should therefore be used with caution in the elderly, in patients with advanced or cardiovascular disease, and in those also being treated with opiates [8]. Different tricyclics and serotoninergic agents are significant inhibitors of the isoenzyme CYP2D6 [101], which catalyzes the conversion of codeine into morphine, and thus may almost completely abolish its analgesic action [22]. There has been a recent interest in phytotherapeutic agents (hypericum extracts) for depression of moderate intensity [74]; no studies have yet been conducted with these substances in palliative care. Finally, mirtazepine, one of the newest agents with both serotoninergic and noradrenergic actions, seems to be well tolerated in the elderly [34], but again has not been studied in the palliative care setting.

Amphetamines (psychostimulants) have also been used for the treatment of depression in palliative care. They are known to improve arousal, energy, ability to concentrate and depressive symptoms [42]. They have a rapid onset of action (within 2 days) and may therefore be useful for patients with limited survival [71]. Several open trials and also randomized double-blind placebo-controlled studies in depressed medically ill patients have led to the conclusion that amphetamines are effective in relieving depressive symptoms, especially in adjustment disorders (but also major depression) and in women [42, 55, 108]. They should not be prescribed to agitated or anxious patients [10, 42]. During the latent period before antidepressants take effect, alternative treatments with benzodiazepines [40, 98] and neuroleptics [63] may also be considered, especially for patients in the terminal phase of their life.

Unresolved issues

Some of the unresolved issues are listed in Table 8. Studies comparing different classes of medications for different clinical situations, such as for rapid relief of symptoms or rapid onset of action until antidepressant treatment is effective, are still lacking, and clinical experiences remain somehow controversial. Such studies with higher numbers of patients would be of great importance, but are not easy to conduct because of recruitment difficulties, drop-outs and intercurrent disease and treatment variables [41]. Finally, various factors hampering effective psychopharmacological treatment remain unknown.

Table 8 Psychopharmacological treatment of depression in palliative care: unresolved issues

Effectiveness studies comparing different agents are still lacking
The value of alternative substances, such as amphetamines, for patients with limited survival times remains unknown
A variety of patient-, physician- and health care-related factors hamper effective pharmacological treatment; yet they have not been identified and targeted in intervention studies

Table 9 Psychopharmacological treatment of depression in palliative care: recommendations

Antidepressants should be utilized without delay once the diagnosis of major depression has been established
Until effectiveness or if survival time is very limited, amphetamines, benzodiazepines and neuroleptics should be considered
Strategies to improve pharmacological treatment should not be conceptualized separately, but should be part of an comprehensive management strategy
Future research should attempt to identify and target factors that hamper effective pharmacological treatment

Recommendations

There is enough clinical and scientific evidence to justify exploiting the benefit of these medications, even in a terminal stage of disease (see Table 9) [14]. Medication should be started without delay, like any other therapy aimed at symptom control. In patients with limited life expectancy, amphetamines may be considered. For the relief of suffering until antidepressants are effective and in anxious and depressed patients, benzodiazepines and neuroleptics may also be useful. Strategies to improve pharmacological treatment cannot be conceptualized separately, but should be part of a comprehensive management strategy based on a proactive but thoughtful approach with due consideration for all aspects of depression in palliative care. Future research should focus on interventions directed at barriers that hamper adequate prescription of antidepressants.

Table 10 Conclusions

– Undertreatment and underdetection of depression in palliative care remains a major problem impairing the quality of life of the patients and their significant others
– A proactive and comprehensive approach should be favored. Such an approach addresses detection and treatment of depression in palliative care and training, and consists in clinical, scientific and educational strategies
– A flexible approach should be adopted to the implementation of general guidelines, depending on the setting
– Close collaboration with specialized mental health professionals is highly recommended
– Clinical experience and scientific evidence should be considered when psychological treatment modalities are implemented
– Studies evaluating different comprehensive approaches should be initiated

Conclusions

Depression in palliative care is a most complex topic, being associated with many unresolved issues as well as a lack of scientific evidence. The major problem remains the underdetection and undertreatment of the disorder, both of which are related to a variety of different factors, only some of which have been identified (Table 10). A proactive approach to this problem should include clinical, scientific and educational aspects and address detection and treatment of depression in palliative care in a comprehensive manner. Such an approach would overcome the shortcomings of isolated actions, which lose their impact in targeting the individual levels of the problem separately. In order to achieve these objectives, interdisciplinary cooperation with specialized mental health professionals from consultation-liaison psychiatry and psychooncology will be necessary.

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